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REVIEW

Effect of tumor necrosis factor inhibitors on interstitial lung disease in rheumatoid arthritis: angel or demon?

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Ying Huang
Weiji Lin
Zhe Chen
Yu Wang
Yao Huang
Shenghao Tu

Institute of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, People's Republic of China

Objectives: This study evaluated the correlation between tumor necrosis factor alpha inhibitor (TNF-I) and interstitial lung disease (ILD) in rheumatoid arthritis (RA). We aimed to raise awareness and consummate therapy by summarizing the characteristics of the adverse events of ILD.

Methods: A comprehensive search of the PubMed, Embase, Ovid, Cochrane, China National Knowledge Infrastructure, and Wanfang databases was performed from inception to November 2018. Statistical analysis of demographic characteristics, clinical features, and relative risks was performed using Microsoft Excel 2007 and SPSS version 20.0.

Results: A total of 7 eligible articles and another 28 case reports were enrolled. The 7 cohort studies demonstrated the tendency that ILD cases might not benefit from TNF-I therapy. TNF-I might be associated with ILD adverse events. The case reports further confirmed these findings, as most (87.5%) of the cases showed that TNF-1 was harmful to patients with ILD and even resulted in a 35% mortality rate. Further investigation revealed that ILD adverse events tended to appear in female patients with a long RA history ($p<0.05$). The subgroup analysis suggested that early detection and precise treatment are key factors in determining survival or death when an ILD adverse event occurs. A large proportion of ILD adverse events (48.6%) appeared at 2.38±1.03 weeks after the infusion of infliximab.

Conclusion: A fresh look at the evidence highlights that TNF-I might be associated with ILD adverse events in RA, which can induce more severe pulmonary symptoms and even result in death. Therefore, more attention should be paid to effective prevention, early diagnosis, and precise management. Notably, further prospective cohort studies are warranted to better interpret the association or causality between TNF-I and ILD.

Keywords: interstitial lung disease, rheumatoid arthritis, tumor necrosis factor inhibitors, adverse effects

Introduction

Interstitial lung disease (ILD) is characterized by diffuse pulmonary parenchyma, alveolar inflammation, and interstitial fibrosis. The incidence of ILD was 20–30% in patients with rheumatoid arthritis (RA) according to the study by Castelino et al.[1] ILD commonly occurs as an extra-articular manifestation of severe RA,[2] and results in high morbidity and mortality.[3,4] Additionally, the prevalence of ILD has been confirmed to increase by 0.3–11% in RA treated with methotrexate (MTX),[5,6] which serves as a reminder that more caution should be taken when using other disease-modifying drugs (DMARDs). Although TNF-I has been widely used in the

Correspondence: Shenghao Tu
Institute of Integrated Traditional Chinese and Western Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Jiefang Avenue 1095, Wuhan 430022, People's Republic of China
Tel +86 27 8366 3402
Email shtu@tjh.tjmu.edu.cn

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past decades, its adverse effects on non-infectious complications (especially ILD) have not been well recognized and warrant investigation.

Initially, we presumed that ILD in patients with RA may benefit from TNF-I because TNF-α plays a pivotal role in the pathogenesis of ILD.[7] A case report from the same period also indicated that TNF-1 has a positive effect on ILD.[8] The results of clinical randomized controlled trials further emphasized that there is no difference compared with other DMARDs in terms of ILD. However, an ever-increasing incidence of adverse events has been reported since the first report of ILD induction by infliximab in 2002 buchong cankao wenxian. The randomized controlled trials performed thus far do not provide enough guidance. Therefore, we performed a systematic literature research and attempted to summarize the commonalities in order to better characterize the magnitude of this problem.

In this review, we discuss the risks of TNF-I use with respect to new onset of RA-ILD, the deterioration of RA-ILD, and the mortality of RA-ILD based on clinical cohort studies and case reports. We attempted to summarize the clinical characteristics of ILD adverse events, and to distinguish ILD secondary to TNF-I therapy from spontaneous ILD. Lastly, we hope to raise more awareness, enhance the diagnosis, improve the therapy, and fill the gaps in current knowledge.

Methods

Search strategy

The PubMed, Embase, Ovid, Cochrane, China National Knowledge Infrastructure, and Wanfang databases were searched using the keywords "etanercept", "infliximab", "adalimumab", "golimumab", "certolizumab pegol", "tumour necrosis factor inhibitors", "anti-TNF", "biologic disease-modifying anti-rheumatic drugs", "lung diseases, interstitial", and "pulmonary fibrosis", for articles published up to November 2018 according to PRISMA guidelines. The relevant references of the selected articles were also hand searched to retrieve additional eligible articles.

Inclusion and exclusion criteria

The studies included in this systematic review had to meet all of the following inclusion criteria: (1) case-control studies, cohort studies, clinical trials, and case reports; (2) Chest CT as used to diagnose ILD, RA was diagnosed according to American College of Rheumatology European Union Against Rheumatism classification criteria for RA (2010) (3) presenting enough information about RA-ILD, TNF-I, and the relationship between them; (4) investigating the risk factors of RA-ILD (age, sex, smoking, antibody seropositivity, and others); and (5)written in the English language. The exclusion criteria were as follows: (1) basic studies, mechanistic studies, review articles, guidelines, and meta-analysis; (2) duplicate data presented in multiple studies, unavailability of full-text articles, and lack of necessary data; (3) included patients less than18 years old or pregnant women, and (4) Except for the simple RA.

Data extraction and statistical analysis

Two authors (Huang and Lin) independently determined the eligible studies according to the aforementioned criteria, extracted the required information, and addressed any discrepancies through a discussion.

Statistical analysis

Statistical analysis was carried out using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) and IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA), Chi-square test was used for statistical analysis.

Results

Literature search

As shown in Figure 1, a total of 1506 articles were identified through the database searching. We scored 1304 studies after the removal of duplicates; 1182 articles not relevant to our topic were excluded out of the systematic review after reviewing the titles. The remaining 122 articles underwent detailed reading of abstracts, among which 78 articles were further excluded according to the inclusion and exclusion criteria. Because 9 of the remaining 44 articles were not available of full-text, it's a pity finally we only get 7 eligible articles (22,981 patients) and another 28 case reports (40 patients). All of the selected studies were published between 2002 and 2018. More details about the eligible articles are provided in Table 1, and details about the case reports are shown in Table 2. We performed a descriptive review rather than a meta-analysis owing to the significant heterogeneity and the limited data.

Controversy and consensus in large-sample studies

As shown in Table 1, Herrinton et al[9] provided evidence that TNF-I does not increase the incidence of ILD in

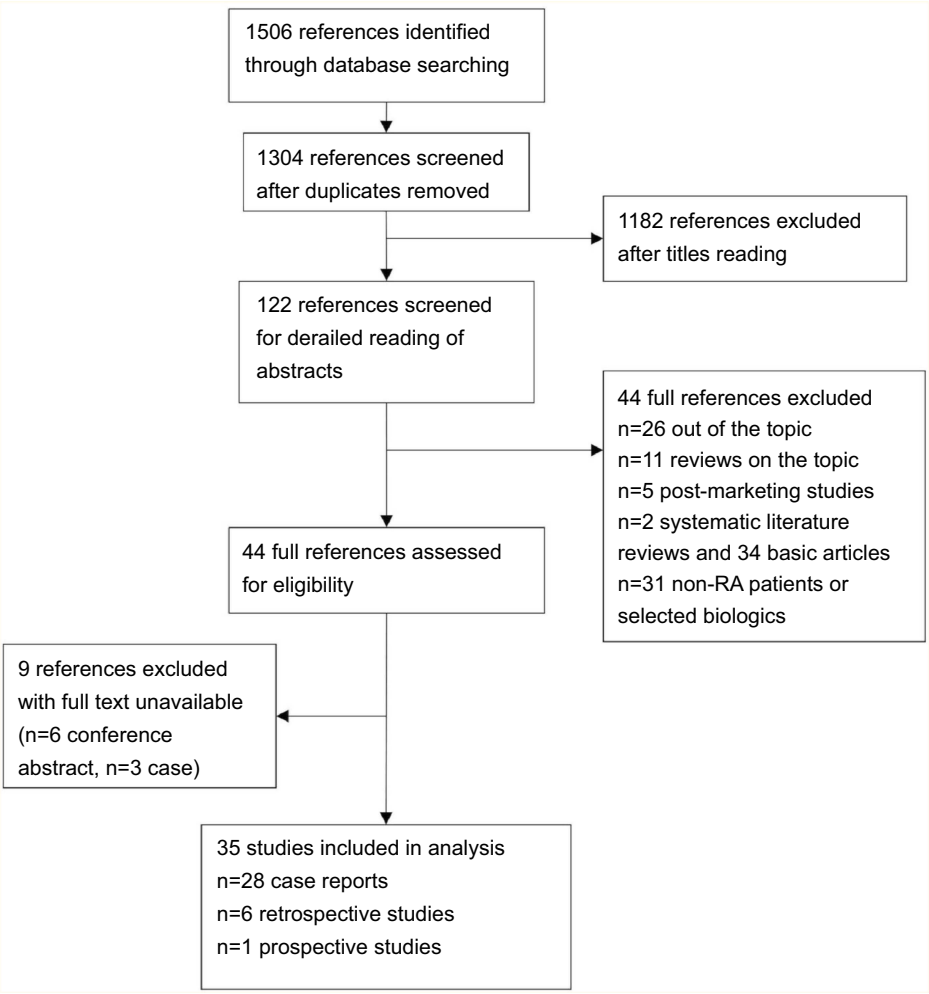

Figure 1 Search parameters and strategies of literature review.

autoimmune diseases, mainly in RA. However, Nakashita et al[10] suggested that TNF-I has the potential risk of inducing ILD and might exacerbate pre-existing ILD compared with non-TNF-I biological therapy. Moreover, their further study[11] emphasized that TNF-I was less effective than abatacept in patients with pre-existing ILD. In the same year, Curtis et al[12] reported that no significant risks of ILD and related complications were observed with TNF-I when compared with T-cell, B-cell, and interleukin (IL)-6 inhibitors. In a small-sample study, Koo et al[13] emphasized that a potential risk of mortality existed in older patients with RA-ILD within months of the initial TNF-I therapy. In 2017, Druce et al[14] hypothesized that patients with RA-ILD using TNF-I had a higher mortality rate than patients using rituximab. Additionally, Detorakis et al[15] compared TNF-I with MTX and then provided supporting evidence for the efficacy and safety of TNF-I according to high-resolution computed tomography (HRCT) evaluation and pulmonary function tests [15]and compared TNF-I with MTX. In short, previous studies demonstrated the tendency that ILD might not benefit from TNF-I therapy.

Noteworthy differences in case reports

As depicted in Table 3, we found that ILD adverse events after TNF-I therapy accounted for 87.5% of the retrieved cases. A 68.57% rate of positivity to rheumatoid factor or anti-cyclic citrullinated peptide antibody was mentioned in the known case reports, and most patients presented an invasive disease. Initially, we speculated that age, sex, RA history, pulmonary history, use of MTX, and the different types of TNF-I led to different outcomes. After the statistical analysis (chi-square test) of retrieved cases, we conjectured that TNF-I is beneficial or harmful to ILD depending on the history of RA and sex ($p<0.05$), rather than age, use of MTX, and other factors. A female preponderance (74.29%) was observed in the spontaneous ILD adverse events, whereas patients treated with TNF-I

Table 1 Cohort studies that assessed TNF-I on ILD in rheumatoid arthritis

Reference	Year	Study design	Research type	Region/ population	Numbers	Data origin	Population	Experimental group	Control group	Objective	Conclusion
Detorakis et al[15]	2017	NA	Prospective	Greece	168	NA	RA	TNF-I	Non-biologic agents	Investigate the efficacy and safety of TNF-I compared to non-biologic DMARDs in RA	No new-onset ILD or exacerbation of preexisting-ILD, especially in patients with TNF-I supporting the efficacy and favorable safety profile of this treatment in RA patients
Druce et al[14]	2017	NA	Retrospective	British	352	NA	RA-ILD	RTX	TNF-I	Compared mortality in patients with RA-ILD who revived RTX or TNF-I as their first biologic	Patients with RA-ILD who received rituximab had lower mortality rates compared to TNF-I
Nakashita et al[10]	2016	Observational study	Retrospective	Japan	62	Single center	RA-ILD	ABA	TNF-I	Possible effect of abatacept on the progression of ILD in RA patients	Abatacept might have a lower risk of worsening preexisting ILD than TNF-I
Koo et al[13]	2015	NA	Retrospective	British	24	NA	RA-ILD	TNF (death)	TNF-I	Evaluate the impact on mortality of TNF-I treatment of RA-ILD	Lung complications can occur within months of initial anti-TNF treatment in older RA-ILD patients and TNF-I should be used with caution in these patients

(*Continued*)

Table 1 (Continued).

Reference	Year	Study design	Research type	Region/ population	Numbers	Data origin	Population	Experimental group	Control group	Objective	Conclusion
Curtis et al[12]	2015	Cohort	Retrospective	America	13,795	Data source	RA	TNF-I	ADA, RTX and CTR	Evaluate ILD incidence and the exacerbation among users of abatacept, rituximab, and tocilizumab compared with anti-TNF agents in adult RA patients	No significant differences in the risk of ILD and its related complications between RA patients receiving TNF-I and MOA agents
Nakashita et al[10]	2014	Case-control	Retrospective	Japan	163	Single center	RA	TNF-I	Non-biologic agent	Assess the risks of TNF-I for patients with ILD	TNF-I have the potential risk of ILD events, particularly for patients with pre-existing ILD
Herrinton et al[9]	2013	Cohort	Retrospective	America	8,417	Kaiser permanent Northern California	Autoimmune disease (RA)	ETA,INF and ADA	MTX	Evaluate the association of TNF-I with risks of ILD/PF among persons with the autoimmune disease compared with non-biologic therapy	Compared to non-biologic therapies TNF-I does not associate with a diagnosis of ILD

Abbreviations: NA, unknown; RTX, rituximab; CTR, tocilizumab; ADA, adalimumab; ABA, abatacept TNF-I, tumor necrosis factor inhibitor; MTX, methotrexate; ILD, interstitial lung disease; PF, pulmonary failure; MOA, alternate mechanisms of action; RA, rheumatoid arthritis; DMARD, disease-modifying drugs; ETA, etanercept; INF, infliximab.

Table 2 Case reports that assessed TNF-I on ILD in rheumatoid arthritis

	1	2	3	4	4	4	5	6	7	7	7
Reference	Peno-Green et al[31]	Vassalo et al[32]	Bargagli et al[19]	Ostor et al[21]	Ostor et al[21]	Ostor et al[21]	Chatterjee[33]	Hennum et al[34]	Ostor et al[26]	Ostor et al[26]	Ostor et al[26]
Year	2002	2002	2004	2004	2004	2004	2006	2006	2006	2006	2006
Age	50	71	70	60	67	75	84	59	49	61	67
Sex	F	M	F	F	M	F	F	M	F	F	M
Smoking	NA	Ex-smoker	Non	NA	NA	NA	Ex-smoker	NA	Non	NA	NA
CCP or RA	Seroposi-tive	Seroposi-tive	NA	NA	NA	NA	Seropositive	Seropositive	Seropositive	Seropositive	Seropositive
RA history	5	3	NA	12	4	33	Longstanding	6	32	12	4
Pulmonary history	NA	Pulmonary fibrosis	Pulmonary fibrosis	Asymptomatic fibrosis alveolitis	Asymptomatic fibrosis alveolitis	Asymptomatic fibrosis alveolitis	No respira-tory symptoms	PF and nodular	No respira-tory history	Mild RA-asso-ciated pul-monary fibrosis	No respira-tory symptoms
Symptoms	Cough and dyspnea	Dyspnea and cough	NA	Breathless	Breathless	Breathless	Fever, breath-less and cough	Dyspnea, cough, and low-grade fever	Dyspnea, cough, and night sweats	Breathless and dry cough	Dyspnea and cough
Onset delay	2 mon	1 year	15 month	2nd	3rd	2nd	2 wks after 2nd infusion	1 wk after 1st	Shortly after the 3rd	3 wks follow-ing 2nd	3 wks after 3rd
MTX	Yes	Yes	No	No	No	No	No	Yes	No	No	No
Type of TNF-I	ETA	INF	INF	INF	INF	INF	INF	INF	INF	INF	INF
Pulmonary history	NA	Pulmonary fibrosis	Pulmonary fibrosis	Asymptomatic fibrosis alveolitis	Asymptomatic fibrosis alveolitis	Asymptomatic fibrosis alveolitis	No respira-tory symptoms	PF and nodular	No respira-tory history	Mild RA-asso-ciated pul-monary fibrosis	No respira-tory symptoms
Outcome	Deteriorate	Improved	Improved	Death	Death	Death	Deteriorate	Death	Recovery	Death	Death

(*Continued*)

Table 2 (Continued).

	7	7	8	9	10	10	11	12	13	13	13
Reference	Ostor et al[26]	Ostor et al[26]	Mori et al[35]	Villeneuve et al[27]	Lindsay et al[36]	Lindsay et al[36]	Schoe et al[37]	Huggett and Armstrong[38]	Kramer et al[13]	Kramer et al[13]	Kramer et al[13]
Year	2006	2006	2006	2006	2006	2006	2006	2006	2002	2002	2002
Age	68	75	66	70	61	64	67	76	63	64	80
Sex	F	F	F	M	F	F	M	F	F	F	F
Smoking	Yes	Ex-smoker	NA	NA	NA	Ex-smoker	Ex-smoker	Non	NA	NA	NA
CCP or RA	Seropositive	Seropositive	Seropositive	Seropositive	NA	Seronegative	Seropositive	Seropositive	Seropositive	Seronegative	Seropositive
RA history	1	33	5	12	10	11	4	3	NA	NA	NA
Pulmonary history	Pulmonary fibrosis	Pulmonary fibrosis	No respiratory symptoms	No respiratory history	Pulmonary fibrosis	COPD but without pulmonary fibrosis	NA	No respiratory symptoms	NA	Nodular	NA
Symptoms	Breathless and dry cough	Breathless, lethargy and dry cough	Fever, headache and hypoxia	Dyspnea, fever, and fatigue	Breathless	Breathless	High fever, cough and dyspnea	Breathless and dyspneic	Dyspnea and hypoxemia	Fever, breathless, dyspnea and hypoxemia	Fever, dyspnea and hypoxemia
Onset delay	3 wks after 3rd	1 wk following 2nd	1 wk after 3rd	9 day after 3rd infusion	6 wks (12 injections)	3 wks (6 injections)	12 wks	10 wks	Soon after 3rd infusion	1 wk after 3rd infusion	3 wks after 3rd infusion
MTX	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Type of TNF-I	INF	INF	INF	INF	ETA	ETA	ADA	ADA	INF	INF	INF
Pulmonary history	Pulmonary fibrosis	Pulmonary fibrosis	No respiratory symptoms	No respiratory history	Pulmonary fibrosis	COPD but without pulmonary fibrosis	NA	No respiratory symptoms	NA	Nodular	NA
Outcome	Death	Death	Recovery	Recovery	Death	Recovery	Deteriorate	Death	Recovery	Recovery	Recovery

(*Continued*)

Table 2 (Continued).

	14	15	16	16	17	17	17	18	19	20	21
Reference	Courtney et al[39]	Hagiwara et al[40]	Tournadre et al[41]	Tournadre et al[41]	Antoniou et al[20]	Antoniou et al[20]	Antoniou et al[20]	Taki et al[42]	Pearce et al[43]	Yamazaki et al[44]	Komiya et al[45]
Year	2006	2007	2007	2007	2007	2007	2007	2009	2012	2010	2011
Age	72	70	42	52	62	64	70	74	71	64	78
Sex	F	F	M	M	M	M	M	F	F	F	M
Smoking	NA	Ex-smoker	Non	Yes	Ex-smoker	Yes	Ex-smoker	NA	Non	NA	NA
CCP or RA	NA	Seropositive	Seropositive	Seropositive	Seropositive	Seropositive	Seropositive	Seronegative	Seropositive	Seropositive	Seropositive
RA history	longstanding	6	12	5	10	2	5	NA	8	18	18
Pulmonary history	No respiratory history	Asymptomatic ILD	No respiratory symptoms	Pulmonary fibrosis	Pulmonary fibrosis	Rheumatoid pulmonary history	Pulmonary history	Pulmonary fibrosis	No respiratory history	No respiratory history	No respiratory history
Symptoms	Dyspnea, hypoxia, and fever	Breathless	Exertional dyspnea	Fever and dyspnea	Dyspnea, cough	Dyspnea, cough	Dyspnea, cough	Severe dyspnea	Breathless and dry cough	Dry cough	Fever and cough
Onset delay	4 wks after 3rd infusion	8 wks	36 wks	4 wks	1 y	1 y	1 y	Soon after 2nd	4 wks	20 wks	A month
MTX	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Type of TNF-I	INF	ETA	ETA	ETA	INF	INF	INF	INF	Cer	ADA	ADA
Pulmonary history	No respiratory history	Asymptomatic ILD	No respiratory symptoms	Pulmonary fibrosis	Pulmonary fibrosis	Rheumatoid pulmonary history	Pulmonary history	Pulmonary fibrosis	No respiratory history	No respiratory history	No respiratory history
Outcome	Death	Stable	Recovery	Stable	Improved	Improved	Improved	Recovery	Deteriorate	Recovery	Recovery

(*Continued*)

Table 2 (Continued).

	22	23	24	25	26	27	28
Reference	Cho et al[46]	Millar et al[47]	Lager et al[48]	Glaspole et al[49]	Dias et al[50]	Migita et al[30]	Watad et al[51]
Year	2012	2012	2013	2013	2013	2017	2015
Age	36	67	72	66	62	68	63
Sex	F	M	F	F	F	F	F
Smoking	Non	NA	Ex-smoker	Non	NA	Yes	Non
CCP or RA	NA	Seropositive	Seropositive	Seropositive	NA	NA	NA
RA history	12	34	43	35	20	15	10
Pulmonary history	NA	MTX-induced pneumonitis history	NA	NA	No respiratory history	Pulmonary fibrosis	NA
Symptoms	Cough	Short of breath	Dry cough and shivering	Breathless and cough	Dry cough, dyspnea and fever	Breathless, dyspnea and dry cough	Dry cough and dyspnea
Onset delay	NA	NA (he failed to Cer until 12 wks)	8 wks	12 wks	1 wk after 2nd	3 wks	16 wks
MTX	Yes	Yes	Yes	Yes	Yes	No	Yes
Type of TNF-I	ETA	Cer	Cer	Cer	ADA	Cer	ETA
Pulmonary history	NA	MTX-induced pneumonitis history	NA	NA	No respiratory history	Pulmonary fibrosis	NA
Outcome	Deteriorate	Death	Stable	Death	Recovery	Recovery	Deteriorate

Abbreviations: F, female; M, male; NA, unknown; ADA, adalimumab; ABA, abatacept; Cer, certolizumab pegol; INF, infliximab; ETA, etanercept. wk(s), week(s); TNF-I, tumor necrosis factor inhibitor; MTX, methotrexate; ILD, interstitial lung disease; PF, pulmonary fibrosis; MOA, alternate mechanisms of actions; RA, rheumatoid arthritis; CCP, cyclic citrullinated peptides; COPD, chronic obstructive pulmonary disease.

Table 3 Noteworthy differences in case reports

	ILD improved (N=5)	ILD induced or deteriorate (N=35)	*p*-Value
Age	67.4±3.56 years	65.23±10.16 years	0.642
Gender (female) (number/ratio)	1(25.71%)	26(74.29)	0.031
History of RA	5±3.56 years	15±4.4 years	0.000
Used of MTX (number/ratio)	3(60%)	24(68.37%)	1.00
Onset of disease	1 year	INF 2–3 wks after 2–3 doses	–
Using INF (number/ratio)	5(100%)	17(48.57%)	0.053
CCP or RF positive (number/ratio)	4(80%)	24(68.57%)	–

Abbreviation: ILD, interstitial lung disease; RA, rheumatoid arthritis; MTX, methotrexate; INF, infliximab; CCP cyclic citrullinated peptides; RF, rheumatoid factor.

included more men. Although all ILD benefits were derived from infliximab antibodies, the performance of infliximab in ILD adverse events showed no significant differences compared with other TNF-I drugs.Therefore, more attention should be paid to pulmonary symptoms when TNF-I is prescribed for long-term use in female patients with RA.

Possible decisive factors for different outcomes

The above results showed that most patients experienced ILD adverse events; however, the outcome was variable. We performed a sub-group analysis (death and survival) of ILD adverse events to explore the decisive factors. The results in Table 4 indicate that deaths accounted for 40% of the ILD adverse event cases. After the analysis of these results with the chi-square test, significant differences were observed in age, pre-existing lung disease, use of antibiotics, and combination treatment with azathioprine ($p<0.05$). Patients who died were older (66 vs 64 years) and had a higher use of antibiotics (77% vs 29%). In addition, the combination of azathioprine was positively associated with death. Although the use of MTX might be a risk factor of ILD adverse events, our results showed that the combination of MTX with infliximab probably did not affect ILD. In addition to the quantifiable results, we speculated that patients who died had a more urgent and severe condition based on the median episode delay. Therefore, early detection and precise treatment may be key factors in determining the chances of survival when an ILD adverse event occurs.

Predictors of the probability of onset

The aforementioned data indicated that timely diagnosis and treatment of ILD might affect outcomes. Therefore, we attempted to identify those predictive features to allow early detection. As shown in Figure 2, infliximab dominance was obvious in both the survival and death groups, whereas

Table 4 Decisive factors of patients receiving TNF-I therapy for different outcomes

		Death (N=14)	Survivors (N=21)	*p*-Value
Age (years)		66.93±5.59	64.10±11.96	0.416
Gender (female)		10 (71%)	16(76%)	1.000
Smoker		2/5(40%)	6/10(60%)	0.608
Combination	INF + MTX	7(50%)	17(81%)	0.073
	INF + AZA	6(43%)	1(5%)	0.010
History of RA		15.15±12.83	14.13±10.30	0.796
Median onset delay		3 wks	8 wks	–
Pre-existing lung disease		11/13 (79%)	6/14(47%)	0.046
Joint symptom Remission		6/8 (75%)	13/14 (93%)	0.527
Causes of death		Pulmonary deteriorate: 8 MSOF:1	–	–
Use of antibiotics		10(71%)	6(29%)	0.018
Without use of prednisolone		2	NA	–

Abbreviations: INF, infliximab; AZA, azathioprine; MTX, methotrexate; RA, rheumatoid arthritis; NA, unknown; MSOF, multiple systems organ failure; TNF-I, tumor necrosis factor inhibitor.

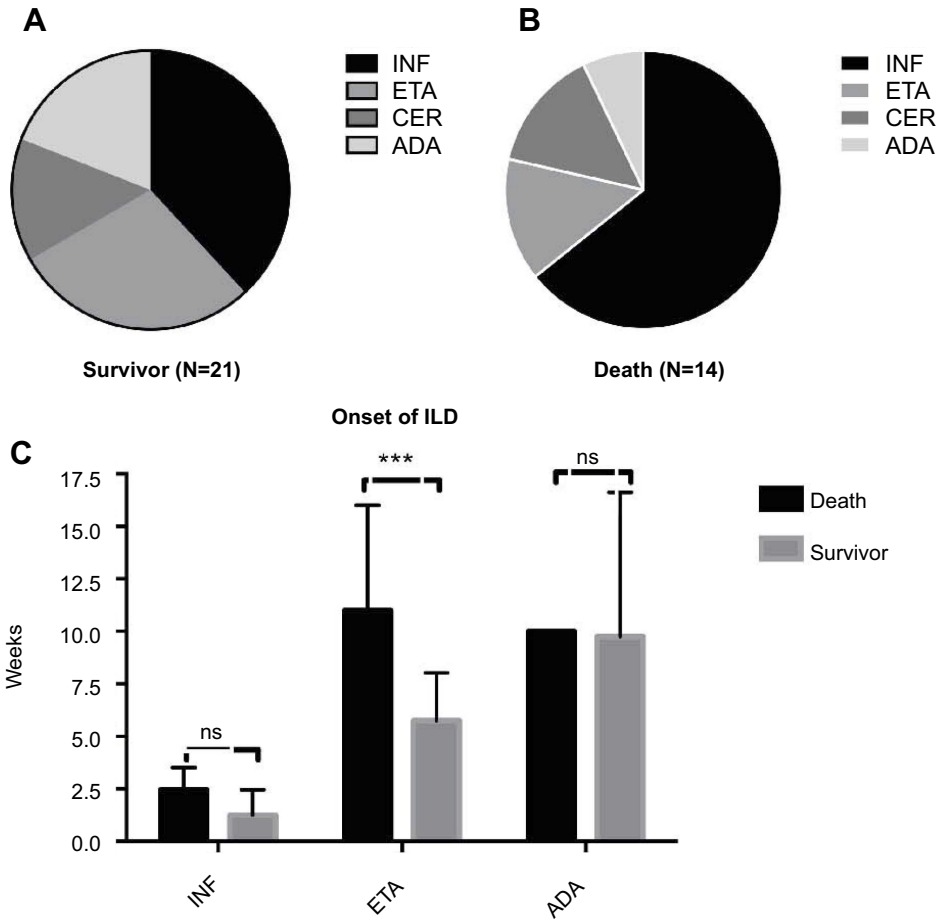

Figure 2 Noteworthy differences in case reports. (**A**) Percentage of different types of biological agents in survivor group; (**B**) Percentage of different types of biological agents in death group; (**C**) Comparison of onset time of different types of biological. ***$p<0.05$.
Abbreviations: ADA, adalimumab; Cer, certolizumab pegol; INF, infliximab; ILD, interstitial lung disease; ETA, etanercept; ns, not significant.

the proportion of adalimumab use was low in the death group. Table 2 demonstrates that the time to death ranged from a few days to 36 weeks; however, Figure 2C shows significant differences between the survivor and death groups in patients treated with etanercept ($p<0.05$). Like acute ILD, the most common clinical manifestations in ILD adverse events cases were shortness of breath and sudden dyspnoea (n=31), followed by non-productive cough (n=17). Further, approximately 10 patients were hospitalized with fever. As HRCT is the cornerstone of ILD diagnosis, we searched for related imaging features. The most common patterns were ground glass and reticulation, which were present in more than half of the patients and tended to be sub-pleural and basilar in distribution (Table 2). Surprisingly, the presence of a distinct honeycomb pattern seems to be relatively rare in ILD adverse events. Therefore, we conclude that patients with typical or atypical disease presenting with the ground-glass pattern after a few weeks of the last infusion are highly suspicious of having ILD.

Management of ILD adverse events

Table 4 indicates that inappropriate use of antibiotics might be associated with death. Thus, there is a need to improve the therapy. Some patients recovered after the timely withdrawal of TNF-I and supplementation with high-dose corticosteroids in the acute period, with tapering to lower doses as necessary depending on the condition. However, the empirical use of broad-spectrum antibiotics and increased dose of antibiotics achieved limited effects. In addition, some patients benefited from home oxygen therapy.

Discussion

Although a better understanding of the pathogenesis of RA and the development of therapies had improved the clinical outcomes in the past decades, the incidence of extra-articular manifestations in patients with RA showed no decrease.[2] A study also indicated that pulmonary involvement occurs in 60–80% patients,[16] and ILD particularly

greatly affects the morbidity and mortality of RA.[3] Substantial health-care use and costs were needed with the increasing prevalence of RA- ILD.[3] Since drug-induced ILD is better than idiopathic ILD in prognosis,[17] there is an urgent need to better identify and avoid the risk factors. As TNF-I is widely used in patients with RA, the safety of TNF-I for ILD needs to be established. In addition to the aforementioned problems, TNF-I-induced ILD not only increases the comorbidities and the mortality rate, but also adds to the difficulty of diagnosis, which, in turn, limits the use of therapeutic drugs. Therefore, we aimed to raise awareness and improve the therapy by evaluating the correlation between TNF-I and ILD in RA.

Previous studies about the relationship between TNF-I and ILD showed controversial results. As TNF-α is known to play a key role in the pathogenesis of ILD,[18] earlier case reports considered that TNF-I had a positive effect on ILD. In 2004, Bargagli et al[16] observed the improvement of pulmonary function with 15 months of infliximab treatment, and another study published in 2007 suggested that infliximab might stabilize the progression of ILD in RA.[20] Clinical results indicated that TNF-I has not increased the incidence of ILD in patients with RA compared with non-biologic therapies[9] or alternative mechanism-of-action agents.[12] However, ever-increasing cases have been reported after the case of fatal exacerbation of RA-ILD in a patient treated with infliximab in 2004.[21] An analysis[22] of 122 cases caught our attention owing to the high incidence of ILD after TNF-I (29%), which is 50 times of that reported in a study using post-marketing surveillance data from Japan (0.6%).[23] A later study demonstrated that the proportion of deaths attributable to RA-ILD was higher in patients treated with TNF-I than in those treated with rituximab,[14] consistent with a cohort study on rituximab.[24]

On the basis of the results, we read the articles and case reports in detail, and found that the controversial results were due to the differences in the population selection, control group, observation period, diagnosis of ILD, and outcome indicators. The current incidence is probably underestimated owing to the rarity of the disease, the short observation period of randomized controlled trials, and the diagnostic methods used to confirm TNF-I associated ILD. The criteria for diagnosing ILD adverse events were as follows: ILD adverse events occurring with an acute or sub-acute lung manifestation shortly after TNF-I infusion with or without remission of articular manifestations, and other related diseases can be excluded on the basis of consistent radiological findings. Notably, patients always do not respond to empiric antibiotic therapy, but symptoms improve when TNF-I is removed. Although the usual interstitial pneumonia pattern accounted for the majority of RA-ILD cases, both pathologically and radiologically,[25] the non-specific interstitial pneumonia pattern was the most common imaging type in TNF-I-associated ILD adverse events. These imaging features indicate an acute onset of ILD that enhances the confidence in the diagnosis. Although azathioprine is the recommended drug for the treatment of RA-ILD, a study[26] highlighted the risk of infliximab in combination with azathioprine.

Additionally, the fact that nearly 40% of patients died indicates that detection and precise therapy should not be delayed. Considering the risks and unforeseen results, we believe that rituximab and abatacept might be better choices than TNF-I agents in patients with pre-existing ILD. Once TNF-I is prescribed to patients with RA, more caution should be taken, especially in older patients with a longer RA history or a rheumatoid-associated pulmonary disease. Respiratory symptoms should be evaluated at follow-up. Pulmonary auscultation is recommended as a routine test. Moreover, high-resolution computed tomography of the lung should be conducted as necessary in the first few infusions of TNF-I. When a patient with RA complained of dyspnoea and dry cough without infectious evidence, withdrawing TNF-I and adding prednisolone are recommended. In the presence of fever, night sweats, and other atypical manifestations, ILD should be distinguished from infectious disease as soon as possible. Hence, more mechanisms should be explored and more randomized controlled studies are needed.

Despite the elucidation of the clinical characteristics of ILD adverse events, the pathogenesis remains unclear. Initially, researchers were reluctant to attribute the lung toxicity to TNF-I itself when TNF-I (mainly infliximab) was as a step-up therapy or used in combination with MTX or azathioprine. Perez-Alvarez et al[22] postulated that TNF-I potentiates the lung toxicity of MTX, which was then confirmed by an MTX study[27] and an azathioprine study.[28] With the ever-increasing use of TNF-I, an increasing incidence of pneumonia toxicity arises. Researchers who considered the status of RA suspected that TNF-I broke the balance (Th1 and Th2, TNF, interferon-γ, and IL-1) and attributed the adverse effects to inflammatory-mediated pathways.[29] As another interesting interpretation, Migita et al[30] speculated that acute exacerbation of RA-ILD treated with certolizumab

was due to NLRP3 inflammation activation. Although we found that the onset of ILD adverse events occurred soon after the last infusion, we supposed that the heterogeneous (mouse) of TNF-I might cause allergic reactions and induce ILD indirectly. The separate analysis of articular and lung manifestations suggested that fast remission might make patients poorly tolerant, with pneumonia as one of the manifestations.

Even with the available evidence, it remains difficult to confirm whether TNF-I is beneficial or harmful to ILD owing to the rarity of the disease. However, the ever-increasing case reports serve as a reminder that TNF-I might induce more severe symptoms, even death. Evidence showing that some patients with RA developed ILD adverse events indicates that doctors should pay more attention during the first few weeks when introducing TNF-I, especially in old female RA patients with pre-existing ILD. Once ILD adverse events occur, precise and timely therapy could be life saving.

Limitations

We acknowledge that the reported risks of TNF-I-induced ILD varied depending on the study population, control group, drug combinations, outcome indicators, and research duration. Moreover, the heterogeneity of ILD (the slice differences between spontaneous and drug-induced ILD) makes it a complex task to interpret the association or causality between TNF-I and ILD. Inevitably, our study has several limitations. First, we attempted to incorporate cohort studies and case reports to increase the power; however, publication bias from the collected articles cannot be excluded. Second, as ILD is a progressive disease, with the first diagnosis occurring after the true incidence, the results of ILD progression might coincide with the TNF-I infusion. Third, because we are overwhelmed with the concern about the occurrence of ILD, the benefit of TNF-I in delaying ILD might have been neglected. Lastly, the assessment of causality is not completely accurate without the mechanisms.

Conclusion

In summary, patients with RA might not benefit from TNF-I in terms of ILD, and more attention should be paid on TNF-I-associated ILD. Early detection and precise treatment are key factors in determining the chances of survival when an ILD adverse event occurs. A prospective study is needed to establish the association or causality between TNF-I and ILD adverse events. The more mechanisms are known, the more therapies will be developed and the more benefits will be achieved.

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Disclosure

The authors report no conflicts of interest in this work.

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